

Patent Claims

1. Use of the expression level of a peptide or polypeptide with a sequence selected from the group consisting of

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- a) an amino acid sequence as presented in SEQ ID NO: 2 or 4;
- b) an amino acid sequence exhibiting a sequence identity with any of the amino acid sequences according to a) of at least 85% over 100 amino acid residues;
- c) a fragment of any of the sequences defined above

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for diagnosis of preeclampsia or a related syndrome.

2. Use of a ligand binding specifically to a peptide or polypeptide with a sequence selected from the group consisting of

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- a) an amino acid sequence as presented in SEQ ID NO: 2 or 4;
- b) an amino acid sequence exhibiting a sequence identity with any of the amino acid sequences according to a) of at least 85% over 100 amino acid residues;
- c) a fragment of any of the sequences defined above

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for diagnosis of preeclampsia or a related syndrome.

3. The use according to claim 2, wherein the ligand is used for measurement of the expression level of the peptide or polypeptide.

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4. The use according to any of claims 1 to 3, wherein the sequence is selected from SEQ ID NO: 8.

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5. The use according to any of claims 2 to 4, wherein the ligand is selected from the group consisting of

- a) KB-R7785 or a derivative thereof;
- b) TIMP-1, TIMP-2, TIMP-3, IGFBP-3, IGFBP-5, HB-EGF, α_2 -macroglobulin, PKC- δ , α -actinin, α -actinin-2, src, Grb-2, or syndecan-4

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- c) antibodies;
- d) nucleic acid or protein aptamers;
- e) fragments or derivatives of any of the substances defined in b), c), or d).

5 6. Use of the expression level of a nucleic acid molecule comprising a nucleic acid selected from the group consisting of

- a) a nucleic acid with a sequence as presented in SEQ ID NO: 1 or 3;
- 10 b) a nucleic acid with a sequence that exhibits a sequence identity with any of the sequences defined in a) of at least 70% over 300 residues;
- c) a nucleic acid which is capable of hybridizing with the nucleic acid as defined in a), or b) under conditions of medium or high stringency;
- d) a nucleic acid with the antisense-sequence of any of the sequences defined in a), b) or c);
- 15 e) a fragment of any of the nucleic acids as defined in a), b), c), or d);
- f) an RNA corresponding to any of the sequences defined in a), b), c), d) or e);

for diagnosis of preeclampsia or a related syndrome.

20 7. Use of a nucleic acid molecule comprising a nucleic acid selected from the group consisting of

- a) a nucleic acid with a sequence as presented in SEQ ID NO: 1 or 3;
- 25 b) a nucleic acid with a sequence that exhibits a sequence identity with any of the sequences defined in a) of at least 70% over 300 residues;
- c) a nucleic acid which is capable of hybridizing with the nucleic acid as defined in a), or b) under conditions of medium or high stringency;
- d) a nucleic acid with the antisense-sequence of any of the sequences defined in a), b) or c);
- 30 e) a fragment of any of the nucleic acids as defined in a), b), c), or d);
- f) an RNA corresponding to any of the sequences defined in a), b), c), d) or e);

for diagnosis of preeclampsia or a related syndrome.

8. The use according to any of claims 6 to 8, wherein the fragment has a sequence consisting of or being part of SEQ ID NO: 7, 13, 14, 15, or 16, or wherein the fragment has a sequence consisting of or being part of SEQ ID NO: 5, 10, 11, or 12.

9. The use according to any of claims 1 to 8, wherein the expression level, ligand, or nucleic acid is used in conjunction with a means or a diagnostic agent for the measurement of expression of any of the genes or proteins selected from the group consisting of

- a) EPAS-1/HIF-2 α ,
- b) neurokinin B
- c) TIMP-1,
- d) VEGFR-1,
- e) VEGF,
- f) IGFBP-1
- g) IGFBP-3,
- h) matrix metalloproteinase-2,
- i) leptin,
- j) PAI-1,
- k) IGF-1,
- l) angiopoietin-2,
- m) decorin,
- n) PlGF,
- o) HLA-G
- p) HB-EGF
- q) TGF- β 3
- r) MIFR-2
- s) LIM
- t) EBI3
- u) one or more of the genes or proteins disclosed in Table 1 or Fig. 6

and/or diagnostic tools for the measurement of blood pressure or protein content of the urine.

10. The use according to any of claims 2 to 9, wherein the nucleic acid, ligand or, additionally, diagnostic agent is present on an array.

11. Use of the nucleic acid molecule as defined in any of claims 6 to 8, or of a peptide or polypeptide comprising a peptide or polypeptide as defined in any of claims 1 to 4 for the identification of ligands binding specifically to said nucleic acid, peptide or polypeptide.
12. A method for the identification of ligands binding specifically to a peptide or polypeptide as defined in in any of claims 1 to 4, comprising the following steps:
- a) contacting the polypeptide with at least one candidate for a ligand;
 - b) measuring the binding of the candidate for a ligand to the polypeptide.
13. A method for diagnosis of preeclampsia or a related syndrome comprising the following steps:
- a) bringing a biopsy or bodily fluid sample into contact with a nucleic acid as defined in any of claims 6 to 8 or a specifically binding ligand as defined in claims 2 to 5, and
 - b) detecting the binding of the nucleic acid or ligand.
14. Use of a nucleic acid as defined in any of claims 6 to 8, or a ligand as defined in any of claims 2 to 5, optionally in combination with a diagnostic agent or diagnostic tool as defined in claim 9, for the manufacture of a diagnostic for the diagnosis of preeclampsia or a related syndrome.
15. A diagnostic containing a nucleic acid or ligand, or, additionally, diagnostic agent or tool as defined in any of claims 2 to 9.
16. A diagnostic kit containing a nucleic acid or ligand as defined in any of claims 2 to 9.
17. The diagnostic or diagnostic kit according to any of claims 15 to 16, wherein the nucleic acid, ligand or, additionally, diagnostic agent is present on an array.
18. Use of a nucleic acid molecule comprising a nucleic acid selected from the group consisting of

- a) a nucleic acid with a sequence as presented in SEQ ID NO: 1 or 3;
- b) a fragment of any of the nucleic acids as defined in a);
- c) a nucleic acid with the antisense sequence of any of the sequences defined in a), or b);
- 5 d) single-stranded or double-stranded RNA, preferably siRNA, with a sequence corresponding to any of the sequences defined in a), b), or c);

for the manufacture of a medicament for the treatment of preeclampsia or a related syndrome.

10 19. The use according to claim 18, wherein the fragment consists of or is located in SEQ ID NO: 5 or 7.

15 20. Use of an inhibitor of the biological activity of a peptide or polypeptide with a sequence selected from the group consisting of

- a) an amino acid sequence as presented in SEQ ID No. 2 or 4;
- b) an amino acid sequence exhibiting a sequence identity with any of the sequences according to a) of at least 85% over 100 residues;
- 20 c) a fragment of any of the sequences as defined above

for the manufacture of a medicament for the treatment of preeclampsia or a related syndrome.

25 21. The use according to claim 20, wherein the fragment has a sequence consisting of or being part of SEQ ID NO: 8.

22. The use according to any of claims 20 to 21, wherein the inhibitor is a disintegrin domain metalloproteinase inhibitor, particularly KB-R7785, a TIMP, particularly
30 TIMP-3 or a fragment thereof, α_2 -Macroglobulin, or an antibody directed against ADAM 12.

23. The use according to any of claims 20 to 22, wherein additionally HB-EGF is used for the manufacture of the medicament.

24. The use according to any of claims 18 to 23, wherein the medicament is for treatment of symptoms of preeclampsia or a related syndrome, particularly for treatment or prevention of intravascular coagulation, blood platelet destruction, placental abruption, or high blood pressure.
25. Use of a nucleic acid, peptide, or polypeptide as defined in any of claims 1 to 8 for identification of an inhibitor of said nucleic acid, peptide or polypeptide, particularly for identification of an inhibitor of the proteolytic activity or substrate-binding activity of said peptide or polypeptide.
26. A method for identification of an inhibitor of the biological activity of a peptide or polypeptide as defined in any of claims 20 to 21, comprising the following steps:
- a) contacting said peptide or polypeptide with a suitable substrate, e.g. HB-EGF,
 - b) measuring the decrease in processing of the substrate in the presence as compared to the absence of a candidate for an inhibitor molecule
27. The method according to claim 26, wherein the candidate for an inhibitor is a substrate or a ligand of a peptide or polypeptide as defined in any of claims 1 to 4.
28. A method for the preparation of a pharmaceutical composition, wherein an inhibitor of the nucleic acids, peptides, or polypeptides as defined in any of claims 18 to 21 is identified according to the methods as defined in claim 26 or 27, synthesized in adequate amounts, and formulated into a pharmaceutical composition.

Summary

The present invention relates to the significant role of ADAM 12, ADAM 12-L, and ADAM 12-S in preeclampsia and related disorders. The invention further relates to the use
5 of said genes and gene products, ligands binding to those, and modulators of activity of the gene products in diagnosis and treatment of preeclampsia and related syndromes. The invention also relates to the use of further genes and combinations thereof in diagnosis of preeclampsia and related syndromes.